

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Families' health care experiences for children with inherited metabolic diseases: protocol for a mixed methods cohort study
AUTHORS	Chow, Andrea; Iverson, Ryan; Lamoureux, Monica; Tingley, Kylie; Jordan, Isabel; Pallone, Nicole; Smith, Maureen; Al-Baldawi, Zobaida; Chakraborty, Pranesh; Brehaut, Jamie; Chan, Alicia; Cohen, Eyal; Dyack, Sarah; Gillis, Lisa Jane; Goobie, Sharan; Graham, Ian; Greenberg, Cheryl; Grimshaw, Jeremy; Hayeems, Robin; Jain-Ghai, Shailly; Jolly, Ann; Khangura, Sara; MacKenzie, Jennifer; Major, Nathalie; Mitchell, John; Nicholls, Stuart; Pender, Amy; Potter, Murray; Prasad, Chitra; Prosser, Lisa A; Schulze, Andreas; Siriwardena, Komudi; Sparkes, Rebecca; Speechley, Kathy; Stockler, Sylvia; Taljaard, Monica; Teitelbaum, Mari; Trakadis, Yannis; van Karnebeek, Clara; Walia, Jagdeep; Wilson, Brenda; Wilson, Kumanan; Potter, Beth

VERSION 1 – REVIEW

REVIEWER	Gagnaniello, Vincenza Padua University Hospital
REVIEW RETURNED	15-Aug-2021

GENERAL COMMENTS	<p>The authors proposed a protocol to understand the health experiences of children with inherited metabolic diseases and their families across Canada. This study is the Phase 1 of a complex four-phase research program to improve family experiences with care. The protocol is well structured and the methods are appropriate.</p> <p>In the abstract it should be mentioned how patients are selected for stage 2.</p> <p>I have some doubts about the patient selection criteria: The study is aimed at children but on line 260 the authors cite adults living with IMD. Please clarify this point. On line 286 it is indicated that children will be eligible if they have an IMD that meets clinical criteria associated with trajectory c, but in table 1 they indicate several disease compatible with trajectory b (e.g. organic acidemias, MSUD, urea cycle disorders, etc). Please clarify this point.</p> <p>The selected diseases are very heterogeneous in relation to the needs of care. I believe that to be representative of real needs, patients should be enrolled approximately in proportion to the incidence of any disease. As indicated by the authors themselves, the selection of patients who have greater access to care could be a major bias that could be avoided.</p> <p>It is not indicated how the "designed parent" is selected. Please clarify this point.</p>
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	Finally, as indicated by the authors, English language may be an important limitation in this study because foreign patients are those with greater difficulty in accessing care. Could a translator solve this problem?
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

The authors proposed a protocol to understand the health experiences of children with inherited metabolic diseases and their families across Canada. This study is the Phase 1 of a complex four-phase research program to improve family experiences with care. The protocol is well structured and the methods are appropriate.

Response: Thank you very much for your general comments on our paper. We have strived to address each of your comments in turn below.

1. In the abstract it should be mentioned how patients are selected for stage 2.

Response: We have added more detail to our description on Lines 119-120.

2. I have some doubts about the patient selection criteria:

The study is aimed at children but on line 260 the authors cite adults living with IMD. Please clarify this point.

Response: Thank you for this question. As part of our patient and public involvement strategy, we have engaged patients and families as investigators and advisors to the study. Although the majority of those involved in this partnership/advisory capacity are parents of children with an inherited metabolic disease (IMD), we wanted to engage a few people who are adults with have IMD themselves and can speak to their own pediatric health care experiences and their own expertise as advocates. We have added a clause to clarify this on Line 263.

3. On line 286 it is indicated that children will be eligible if they have an IMD that meets clinical criteria associated with trajectory c, but in table 1 they indicate several disease compatible with trajectory b (e.g. organic acidemias, MSUD, urea cycle disorders, etc). Please clarify this point.

Response: We are pleased to explain this further. The full eligibility criteria in relation to IMD are described on Lines 284 – 289 and in Table 1. There are 2 main criteria:

- i. Eligible children may have an IMD as described on Lines 284 – 286: “Children with any of 30 priority IMDs included in an existing Canadian pediatric cohort study that will serve as one potential recruitment source[54,55] are eligible for this study.” This criterion is related to the diseases listed in Table 1, number 1, starting with “...identified in the following list:...” and which include the diseases associated with trajectory B that you have mentioned.
- ii. Eligible children may have an IMD as described on Lines 286 - 289: “Few of the IMDs included in that cohort study, however, are characterized as following trajectory (c). Thus, children will also be eligible for this study if they have an IMD that meets clinical criteria associated with trajectory (c) (Table 1), to be evaluated by clinician investigators on a case-by-case basis.” This criterion is related to the diseases listed in Table 1, number 2: “...or meets the following clinical criteria: involves at least three organ systems and chronic

complications of the disease get progressively worse over time, even with available treatment.”

We have added further explanation to Table 1 to clarify the IMD eligibility criteria.

4. The selected diseases are very heterogeneous in relation to the needs of care. I believe that to be representative of real needs, patients should be enrolled approximately in proportion to the incidence of any disease. As indicated by the authors themselves, the selection of patients who have greater access to care could be a major bias that could be avoided.

Response: This is an insightful concern. Indeed, it was difficult to balance generalizability and maximization of data collection in planning this study. The reason that we decided to select our sample using a maximum variation approach is because we want to collect data from families of children with IMD who use the health care system across a breadth of experiences, in order to begin to understand how we might help to improve those experiences for the full range of children with IMD who actually use the system. If we aimed for proportional representation of IMD in our study, we would potentially enroll a lot of children whose IMD are relatively well-controlled, such as the more common IMDs typically considered chronic and non-progressive (e.g., those with phenylketonuria); or who may not have any care encounters in the relatively short – four month – data collection period, such as children with the more common IMDs typically considered acute and episodic (e.g., medium chain acyl-CoA dehydrogenase deficiency). Conversely, children with IMD that typically are considered multi-system and progressive often have rare conditions (<1% of the inherited metabolic disease population in Canada), but have complex needs and high health care use. In a proportionate sampling approach, we would enroll few of these children and thus miss out on the most frequent health care users.

We are taking a maximum diversity approach that includes a goal of achieving variation in enrollment across IMD, which means that we will enroll a range of IMD, including those who may not expect to have frequent health care encounters in the data collection period. We are also aiming for balance between the three IMD ‘groups’ (chronic and non-progressive, acute and episodic, and multi-system and progressive) to ensure representation among these common trajectories of clinical care.

As you mentioned, we address the potential bias of our sampling decision on Lines 528 – 532 in the Discussion. We also aim to address these biases in our data analysis, as described on Lines 445 – 452, by including IMD clinical trajectory group as a planned predictor of satisfaction with health care encounters.

We appreciate your insight that children with infrequent encounters may also include those who have lower access to care and we would not want to systematically exclude this group. Canada has a publicly funded health care system but it is the case that not all health care services are included (e.g., some families may have greater access to support from allied health care providers through private insurance). Access to care is an area of focus of the study and by ensuring to include children with less frequent encounters as well as those who receive care more often we hope to provide insight into this. We have added this to our Discussion (Lines 532 – 535).

5. It is not indicated how the “designed parent” is selected. Please clarify this point.

Response: Thank you. We have clarified that the family selects which parent will be the Designated Parent on Line 276.

6. Finally, as indicated by the authors, English language may be an important limitation in this study because foreign patients are those with greater difficulty in accessing care. Could a translator solve this problem?

Response: We agree that the linguistic limitations may pose a barrier to the participation of some families, particularly newcomers to Canada. Unfortunately, the study is not financially resourced to translate all of the study instruments; the questionnaires are composed of tens of thousands of fields given the degree of automatic 'branching' required to cover all types of encounters. In addition, participants are enabled to complete study instruments at home, at a convenient time for them, instead of in clinic. This attempt to make study participation easier for families, given the study length and the high frequency (weekly) of questionnaire completion required, also makes it impossible to deploy a translator, even if financial resources were not a limitation. We agree that this is important, and as mentioned, have identified this potential limitation in our Discussion, on Lines 524 – 527.

Thank you again for your comments and engagement with our study protocol.